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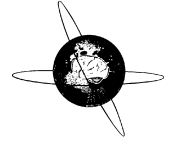
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# Local changes in computational non-rapid eye movement sleep depth in infants



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## HIGHLIGHTS

- The EEG-based quantitative sleep depth analysis shows age-dependent changes in young infants.
- Young infants have local sleep depth differences.
- The local sleep depth differences probably correlate to cortical maturation.

## ABSTRACT

**Objective:** Deep NREM sleep and its hallmark EEG phenomenon slow wave activity (SWA) are under homeostatic control in adults. SWA is also locally regulated as it increases in the brain areas that have been used intensively. Moreover, in children, SWA is a marker of cortical maturation. In the present study the local properties of NREM sleep depth were evaluated using the quantitative mean frequency method. We aimed to study if age is related to NREM sleep depth in young infants. In addition, we studied if young infants have local differences in their NREM sleep.

**Methods:** Ambulatory over-night polysomnographies were recorded in 59 healthy and full-term infants at the age of one month. The infants were divided into two age groups (<44 weeks and ≥44 weeks) to allow maturational evaluations.

**Results:** The quantitative sleep depth analysis showed differences between the age groups. In addition, there were local sleep depth differences within the age groups.

**Conclusions:** The sleep depth change with age is most likely related to cortical maturation, whereas the local sleep depth gradients might also reflect the use-dependent properties of SWA.

**Significance:** The results support the idea that young infants have frontal cortical processing.

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## 1. Introduction

Newborns and young infants spend most of their time sleeping, and the quality of sleep has been found to be important for their development. Although the contribution of each sleep stage is different, both REM and NREM sleep have important functional roles in brain maturation and in normal synaptic development (Graven, 2006). As for NREM, deep NREM is considered to be the most

important sleep stage for infants. In adults, slow wave sleep and slow wave activity (SWA) of NREM sleep are homeostatically regulated and considered a measure of sleep pressure (Borbély and Achermann, 1999). On the other hand, SWA is also a local phenomenon that is known to increase locally at the brain area that has been in intensive use or after learning a specific task (Kattler et al., 1994; Huber et al., 2004). Correspondingly, it has been shown that those cortical areas that have been used less present decreased SWA during subsequent sleep (Huber et al., 2006). These use-dependent features of SWA reflect the important function of NREM sleep in learning, synaptic plasticity, and in homeostatic brain restoration. Moreover, in children, SWA is considered to

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reflect brain maturation in terms of increased synaptic density and developing plasticity (Kurth et al., 2010). The maturation of the brain follows a posterior-anterior trend in that the occipital areas mature first and the frontal areas last (Kurth et al., 2010; Shaw et al., 2008). Furthermore, SWA has been shown to increase locally over maturing brain regions (Kurth et al., 2010), predicting the maturation of skills (Kurth et al., 2012). Accordingly, the local deep sleep and SWA properties of children have usually been studied in the context of cortical maturation with an emphasis on posterior-anterior changes with age (Bosch-Bayard et al., 2012; Buchmann et al., 2011; Fetting et al., 2014; Kurth et al., 2012). Even if there is a growing body of evidence that at least some sensory input is processed cortically in the frontal areas in a newborn (Sakotani et al., 1999; Sanders et al., 2002; Schriever et al., 2014; Taga et al., 2003; Zaramella et al., 2001), it has been presented that the frontal maximum of SWA does not evolve until adolescence (Kurth et al., 2010).

In the present study, we aim to find out if young infants have local differences in their NREM sleep EEG and if these local differences might support the idea of the supposed frontal cortical processing. Moreover, we aim to study if age is related to NREM sleep depth in the young infants.

## 2. Methods

As a part of the CHILD-SLEEP STUDY (Paavonen et al., 2017), a multidisciplinary project comprising 1671 infants born at Tampere University Hospital during 4/2011–2/2013, 88 ambulatory overnight polysomnographies (PSG) were recorded at the age of one month. The study protocol and the inclusion criteria for the PSG study are described in detail in our previous work (Satomaa et al., 2016). In short, the recruited infants were born full-term and healthy. The overnight PSGs were recorded with Embla Titanium equipment according to the usual bed time schedule of each family. A PSG technician visited the homes of each family to attach and remove the electrodes. The following signals were recorded: 6 channels of EEG (F4–, C4–, O2–A1; F3–, C3–, O1–A2), EOG (right and left), submental EMG, oxygen saturation (pulse oximeter, Nonin, with a two-beat averaging time) with waveform, thoracoabdominal inductance plethysmography, diaphragmatic and abdominal EMG, Emfit mattress sensor, ECG, and oronasal thermistor (Dymedix). The nasal pressure transducer was omitted from the protocol to minimize the sleep-disturbing effects of the recording equipment (Goodwin et al., 2001). The sampling rate for the EEG signals was 256 Hz. The Ethical Committee of Pirkanmaa Hospital District and the City of Tampere approved the study (R11032). The parents of all the recruited infants gave their written informed consent.

### 2.1. Participants

In total, 88 healthy and full-term one-month-olds were recorded. The sleep parameters of 84 of these 88 infants are discussed in our recent work. In the present study, 29 recordings (33%) were not included due to technical failures of one or more EEG channels. Therefore, the study sample comprised 59 infants (32 girls and 27 boys) whose conceptional age at birth was on average 40.1 weeks (38.6–41.7 weeks). At the time of the recording, the mean conceptional age of the infants was 44.6 weeks (42.4–48.4 weeks).

To evaluate the effect of age on the quality of sleep, the children were divided into two groups based on age at the time of recording. A cut-off point of one month (44 weeks) was chosen, because the same division had been used in the previous study on the same cohort of infants (Satomaa et al., 2016). The younger group comprised 21 infants (36%) who were less than 44 weeks of age at

the time of recording (younger group, mean age 43.2 weeks, range 42.4–43.9 weeks). Of these, 9 (43%) were boys. The second group comprised 38 infants (64%) who were 44 weeks of age or older at the time of recording (older group, mean age 45.5 weeks, range 44.0–48.4). Of these, 18 (47%) were boys.

### 2.2. Visual analysis

The PSGs were scored into the sleep stages by two independent clinical neurophysiologists (ALS, SLH) with an agreement of 80.3% (range 72.2–90.0%) and kappa score of 0.73 (range 0.58–0.86) indicating substantial agreement (Landis and Koch, 1977). The sleep stages were scored according to the AASM 2012 scoring manual (Berry et al., 2012) as closely as possible. However, due to the age-related sleep-EEG features of the infants, some modifications were implemented (see Satomaa et al., 2016). The infant's state was scored as active sleep (AS), quiet sleep (QS), indeterminate sleep (IS), or wakefulness (W). The cortical arousals were visually scored according to the current guidelines (Grigg-Damberger et al., 2007; Iber et al., 2007; IPWG, 2005). The respiratory events were scored according to the pediatric rules in the AASM manual (Berry et al., 2012; Iber et al., 2007). Because the visual scoring was completed in 2013, and because the same visual analysis was used in our previous work on the same cohort, the 2016 AASM rules (Berry et al., 2015) were not used. The numbers of each type of respiratory events divided by total sleep time (TST) were expressed as respective respiratory event indices (n/h).

### 2.3. Computational sleep depth analysis

In the present work, computational sleep depth was quantified by means of computational EEG mean frequency. The deeper the physiological sleep, the lower are the obtained mean frequency values and vice versa. (Huupponen et al., 2009, 2011; Penzel et al., 1991; Saastamoinen et al., 2006). First, mean frequency values were computed from each of the six EEG channels at 1-s time-resolution by applying the method described in our previous work (Huupponen et al., 2009, 2011). This computing step provided six overnight mean frequency curves with values ranging from 0.5 Hz to 30 Hz.

Two types of computational parameters were then determined on the basis of the mean frequency curves. The combined QS + IS sleep of the one-month-olds was considered a precursor of NREM sleep and termed NotREM sleep. In the present study, only NotREM sleep was taken into account in the analyses. As the first parameter type, the median of the mean frequency values during the NotREM sleep time were extracted from each EEG channel. Then, each mean frequency curve (in its total length) was smoothed using a sliding 31-s long median filter as described previously (Huupponen et al., 2009, 2011; Saastamoinen et al., 2007). As the second parameter type, the deep sleep percentage (DS%), providing the share (in percentage) of the NotREM time containing deeper sleep than the threshold (2 Hz and 4 Hz), was extracted from each smoothed mean frequency curve. The resulting deep sleep percentage parameters were denoted DS2% and DS4%, respectively.

### 2.4. Statistics

Statistical comparisons were performed with SPSS software (v 21). The data were tested for normal distribution with the Kolmogorov-Smirnov and Shapiro-Wilk tests, and all parameters were not normally distributed. The sleep depth parameters were compared between the groups with the nonparametric Mann-Whitney U-test. In addition, the local sleep depth parameters were studied within the groups. The left-to-right and anterior-posterior comparisons of sleep depth parameters within the age groups were

performed with the nonparametric Wilcoxon Signed Ranks test. The multiple comparisons were Bonferroni-corrected. P-values <0.05 were considered statistically significant.

### 3. Results

The visually scored sleep EEG parameters did not differ between the two age groups (Table 1). The only statistically significant difference in the respiratory parameters was found in OAH1: the infants in the younger age group had statistically more obstructive apneas and hypopneas, although the obstructive events were very rare in both groups.

AS%, QS%, IS% = the duration of each sleep state divided by total sleep time (TST). Awakening index and arousal index = the number of awakenings divided by TST and the number of awakenings + cortical arousals divided by TST, respectively. AHI = number of all apneas and hypopneas/h. OAH1 = n of obstructive and mixed apneas and hypopneas/h. ODI3 = Oxygen desaturation index, the number of oxygen desaturations  $\geq 3\% \times 60/\text{TST}$ .

The computational sleep depth parameters, reflecting local sleep depth at the six different EEG locations, of both age groups are presented in Figs. 1–3. The older age group had statistically lower median sleep depth than the younger age group at every EEG channel during the NotREM time (Fig. 1). DS4% was abundant in both groups; however, the older group presented higher DS4% values than the younger group at F4-, C3- and O1-channels (Fig. 2). In addition, the older age group showed higher DS2% values than the younger group at all EEG locations (Fig. 3). Moreover, the local sleep depth measures were studied within the age groups. Neither age group showed any inter-hemispheric differences in any of the computational sleep depth measures. Instead, anterior-posterior (AP) comparisons within the hemispheres revealed several significant differences.

In the younger age group, the median sleep depth was lowest occipitally in the left hemisphere, whereas no significant differences were obtained in the right (Fig. 1). In the older age group, the median sleep depth was lowest frontally in the right hemisphere, whereas no significant differences were found in the left. The amount of DS4% did not show any significant AP differences in either of the groups (Fig. 2). In the younger age group, DS2% was higher occipitally than centrally in the left hemisphere (O1 vs. C3). In the right hemisphere, DS2% was higher frontally than centrally (F4 vs. C4, Fig. 3). In the older age group, DS2% was highest frontally in the right hemisphere.

The inter-group anterior-posterior differences in sleep depth were studied statistically within each hemisphere. This was performed by comparing the sleep depth parameters at each electrode position of the left hemisphere in the younger group to each

electrode position of the left hemisphere in the older group. The same evaluation was performed on the right hemisphere. The resulting statistically significant parameters are presented in Table 2. The absolute values of the tested parameters are presented in the Figs. 1–3.

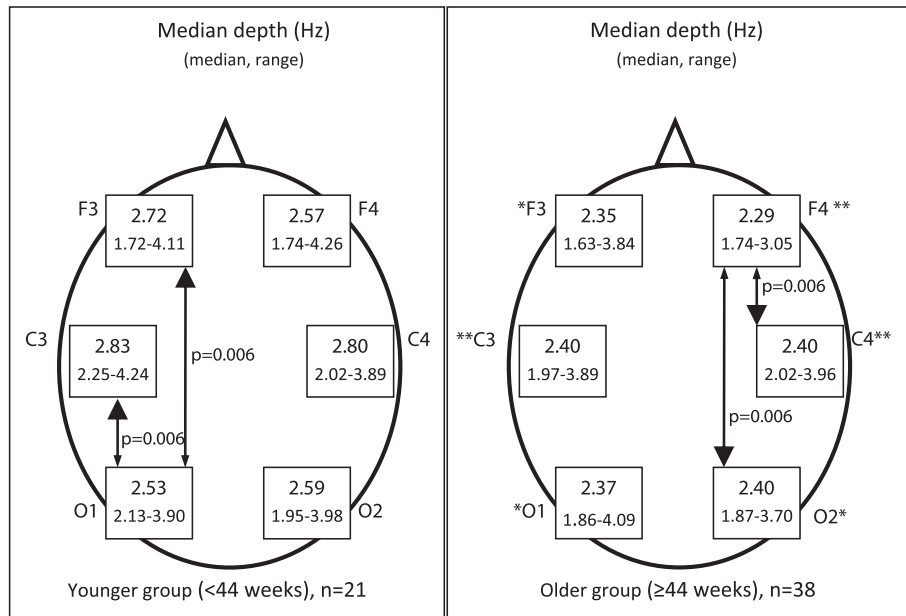
### 4. Discussion

As in our previous study, the visually scored sleep stage percentages or arousal indices did not differ between the two age groups (Satomaa et al., 2016). However, the computational sleep depth analysis of NotREM sleep revealed several differences between the two age groups. Compared with the younger group, the older age group had significantly lower median depth and a higher amount of DS2% at every EEG channel. In addition, this group presented more DS4% frontally in the right and centrally and occipitally in the left hemisphere than the younger age group.

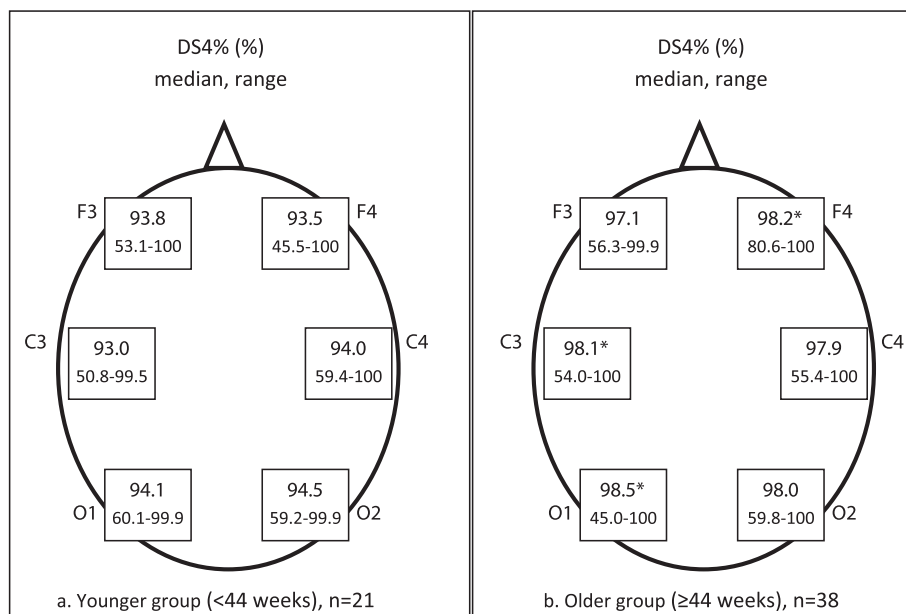
To date, there have only been a handful of studies on the maturational changes of slow EEG frequencies during NREM sleep in the neonatal age group. Topographic evaluations on very young infants are especially scarce even if multichannel recordings have been performed (Chu et al., 2014; Korotchkova et al., 2009; Mandelbaum et al., 2000; Novelli et al., 2016; Otero et al., 2011; Pereda et al., 2006). Moreover, the number of infants in these studies has often been 21 or fewer (Chu et al., 2014; de la Cruz et al., 2007; Fattinger et al., 2014; Jenni et al., 2004; Mandelbaum et al., 2000; Novelli et al., 2016). In addition, only short periods of sleep ranging from some minutes to sixty minutes have commonly been analyzed (Bosch-Bayard et al., 2012; Chu et al., 2014; de la Cruz et al., 2007; González et al., 2011; Korotchkova et al., 2009; Ktonas et al., 1995; Mandelbaum et al., 2000; Pereda et al., 2006; Sankupellay et al., 2011), and the evaluated periods have often represented only daytime sleep (Chu et al., 2014; Korotchkova et al., 2009; Mandelbaum et al., 2000; Otero et al., 2011; Pereda et al., 2006). To the best of our knowledge, the only multichannel work that has used whole night recordings in the infant age group is a study by Novelli and co-workers (2016). They studied the EEG power spectra of 39 children aged between 0 and 48 months at eleven scalp locations during NREM sleep, but only the first 60 min were taken into account. The youngest group comprised 14 infants (0–3 months). They report that delta activity has a stable prevalence at occipital and parietal brain areas across the age groups. Two other quantitative maturational studies (Jenni et al., 2004; Sankupellay et al., 2011) of the newborn age group should also be mentioned, even though their focus was not topographical. Jenni et al. (2004) studied power spectrum at the C4-P4 EEG channel during over-night sleep. Seven infants were studied at two weeks of age and seven at two months of age. The

**Table 1**  
Comparison of sleep parameters of infants in the younger and older age groups. The p-values refer to statistical differences between the age groups; the statistically significant p-values are in italics and bolded.

	Younger group <44 weeks (n = 21)			Older group ≥44 weeks (n = 38)			P
	Median	Range	SD	Median	Range	SD	
Age (weeks at recording)	43.1	42.4–43.9	0.5	45.4	44.0–48.4	0.9	<b>0.000</b>
TST (min)	486.5	366.5–628	60.9	496	380–592	49.1	0.063
QS%	40.5	34.9–54.6	4.5	41.2	30.3–57.2	5.6	0.704
IS%	21.2	9.7–36.0	6.2	21.0	12.5–35.4	6.0	0.537
AS%	37.1	26.5–47.5	6.7	36.6	27.5–54.1	6.7	0.987
Awakening index (n/h)	9.2	5.9–13.0	1.9	7.9	4.8–13.3	2.1	0.087
Arousal index (n/h)	20.3	13.5–25.3	3.0	18.0	12.1–29.0	3.8	0.200
AHI (TST) (n/h)	13.5	1.4–81.7	19.3	8.5	0.5–63.8	13.7	0.093
CAI (n/h)	11.6	1.4–79.8	18.9	8.3	0.5–59.2	13.0	0.226
OAH1 (n/h)	0	0–0.3	0.1	0	0–0.0	0.0	<b>0.018</b>
ODI3 (n/h)	20.9	7.2–79.5	21.8	15.1	0.6–75.5	16.3	0.111



**Fig. 1.** Median sleep depth (with range, in Hz) at different EEG-locations. Smaller value indicates deeper sleep. (a) the younger age group, (b) the older age group. At all channels, the median depth was lower in the older age group than in the younger group (\* = p-value between the groups <0.05, \*\* = p-value between the groups ≤0.01, \*\*\* = p-value between the groups ≤0.001). The arrows denote the statistically significant anterior-posterior differences within the groups.

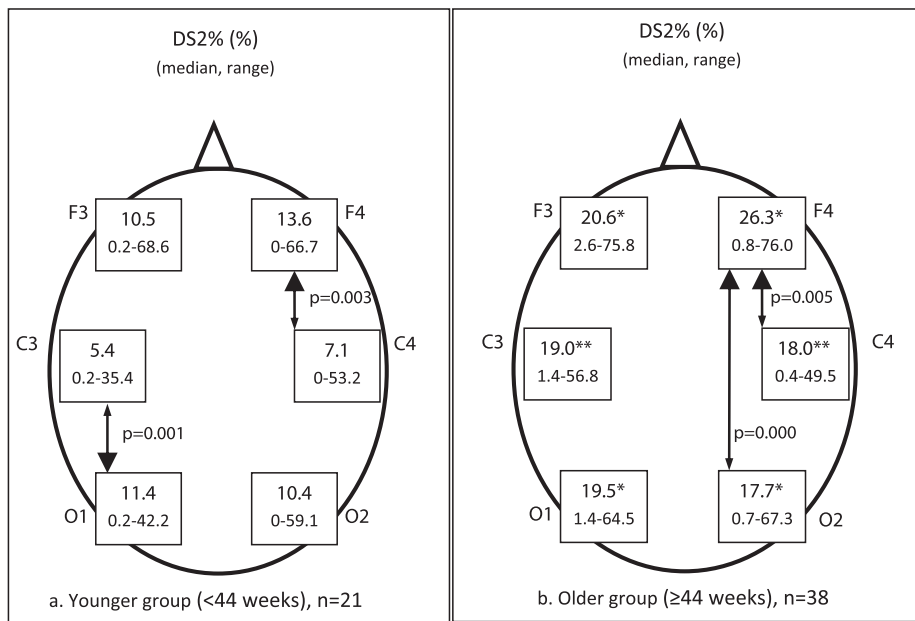


**Fig. 2.** DS4% (with range, in percentages) at different EEG-locations. (a) the younger age group, (b) the older age group. DS4% was higher at C3, O1 and F4 in the older group than in the younger group (\* = p-value between the groups <0.05, \*\* = p-value between the groups ≤0.01, \*\*\* = p-value between the groups ≤0.001). There were no significant local (AP or inter-hemispheric) differences in DS4% within either group.

power spectral changes in consecutive NREM cycles during the night were described. They found that at the age of two months the low frequency delta activity (0.75 Hz–1.75 Hz) presents an alternating pattern being high in every other NREM episode. Sankupellay et al. (2011) studied power spectrum at one central EEG channel during 15 min of nocturnal sleep. Of the 31 subjects studied, the youngest were two weeks of age, and the change in the power spectrum from two weeks to three months of age was described. Delta bandwidth power was found to dominate and increase during QS/N3 NREM from 2 weeks of age to two years.

Because the methods, subjects' age, EEG sample selection, and the electrode set-up varied substantially in the above mentioned studies, the general view of the quantitative slow EEG properties in newborns is rather fragmentary. A consistent finding, however, is that most of a newborn's sleep EEG power is in the delta range (González et al., 2011; Korotchikova et al., 2009; Mandelbaum et al., 2000; Pereda et al., 2006; Sankupellay et al., 2011). This finding was also evident in our study. It has been reported that delta activity increases during early infancy (Chu et al., 2014; Jenni et al., 2004; Pereda et al., 2006; Sankupellay et al., 2011), and the





**Fig. 3.** DS2% (with range, in percentages) at different EEG-locations. (a) the younger age group, (b) the older age group. At all channels, DS2% was higher in the older group than in the younger group (\* = p-value between the groups <0.05, \*\* = p-value between the groups ≤0.01, \*\*\* = p-value between the groups ≤0.001). The arrows denote the statistically significant anterior-posterior differences within the groups.

**Table 2**  
The anterior-posterior sleep depth differences between the two age groups. The statistically significantly differing parameters for each compared electrode pair are presented. The absolute values of these parameters are presented in the Figs. 1–3. (med = median sleep depth).

		Younger group					Younger group		
		F3	C3	O1			F4	C4	O2
Older group	F3	Med, DS4%, DS2%	Med, DS2%	Med	Older group	F4	Med, DS4%, DS2%	Med, DS4%, DS2%	Med, DS4%, DS2%
	C3	Med, DS4%, DS2%	Med, DS4%, DS2%			C4	Med	Med, DS2%	Med, DS4%, DS2%
	O1	Med, DS4%, DS2%	Med, DS4%, DS2%	Med, DS4%, DS2%		O2	Med	Med, DS2%	Med, DS2%

the findings of these previous studies, a posterior dominance of deep sleep would have been expected in the present study, too. Indeed, in the younger age group, the left hemisphere showed slower activity occipitally compared with the more anterior areas, and DS2% was more abundant occipitally than centrally.

In the present study, the anterior-posterior differences were also studied between the age groups. In the left hemisphere, F3 and C3 electrodes of the younger group differed significantly from F3, C3, and O1 electrodes of the older group by all studied parameters – median sleep depth was lower and DS2% and DS4% higher in the older group. However, O1 electrode of the younger group differed significantly from O1 of the older group (median depth, DS2%, DS4%), but not from C3, and from F3 by median depth only. This emphasizes the finding of relative slowness of the left occipital area in the younger group, as it was slow enough not to differ globally from the more anterior electrodes of the older group.

The older age group presented relative slowness of the right frontal area when compared with more posterior areas. This gradient within the right hemisphere manifested in both median sleep depth values and DS2% amounts. The younger age group also showed the relative local slowness of the right frontal area, but the difference was only significant when compared with the right central area and it only visualized in DS2%. Right frontal area stands out also in the inter-group anterior-posterior comparisons. Whereas C4 and O2 of the younger group differed by all studied sleep depth parameters from F4, C4 and O2 of the older group, F4 of the younger group differed from C4 and O2 of the older group by median depth only. This supports the finding of relative slowness in the right frontal area already during the first month of life.

Although the myelination of the frontal cortex is generally assumed to take place late, there are a few reports of frontal cortical responses to sensory stimulation in newborns. For example, exposure to olfactory stimuli is known to induce a frontal EEG activation in infants (Sanders et al., 2002). Olfactory event-related potentials (ERPs) are recordable in the majority of cooperative infants, and they localize frontally (Schriever et al., 2014). Moreover, hemodynamic responses to visual (Taga et al., 2003) and auditory (Zaramella et al., 2001) stimulation have been found frontally in the neonatal period. Therefore, the local enhancement of slow activity in the right frontal area in the present study could also be use-dependent in origin.

The quantitative method used in this study evaluates the mean frequency of EEG. Thus, compared to the conventional SWA power spectrum analysis, the mean frequency method gives additional information about sleep EEG, and it describes a wider frequency range. Another quantitative approach, the period amplitude analysis, is also known to produce more detailed information about frequency and amplitude than the SWA method (Ktonas and Gosalia, 1981). Neither the SWA nor the mean frequency approach is immune to EEG artifacts, e.g., eye and body movement artifacts. However, contrary to the visual and inherently subjective artifact removal required in the SWA analysis, in the quantitative mean frequency method no preprocessing or artifact removal is required. The median operation is the most effective part in minimizing the effects of EEG artifacts (Huupponen et al., 2009). We have previously shown that mean frequency measure correlates well with visual sleep staging (Huupponen et al., 2009, 2011; Saastamoinen et al., 2006, 2007).

## 5. Conclusion

Even though conventional visual scoring did not show any differences between the younger and older age groups in this study, the quantitative sleep depth analysis of NotREM sleep changed with age. Moreover, the one month old infants showed local sleep

depth differences, which also changed with age. Most of the age-dependent sleep depth change probably relates to cortical maturation. Some of it, however, might also reflect a use-dependent local increase of sleep depth. The local findings also support the idea that even very young infants have frontal cortical activity.

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## Conflict of interest statement

None of the authors have potential conflicts of interest to be disclosed.

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